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Short communication

High dose intermittent ticarcillin–clavulanate administration in pediatric cystic fibrosis patients

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Abstract

Background: The Intermountain Cystic Fibrosis Pediatric Center utilizes ticarcillin–clavulanate 400 mg/kg/day divided every 6 h, (maximum 24 g/day). This dosing strategy is higher than the Cystic Fibrosis Foundation (CFF) recommendations and the Food and Drug Administration (FDA) approved package labeling. The purpose is to determine the safety of this dosing regimen.
Methods: A retrospective study of pediatric cystic fibrosis (CF) patients admitted from January 1, 2005 to December 31, 2009 who received the dosing regimen for at least 7 days. Baseline and follow-up laboratory parameters were recorded. Statistical analysis was performed.
Results: 127 patients met inclusion criteria. The mean (±SD) ticarcillin dose was 3.5 g (±2.16) every 6 h; while the mean (±SD) total ticarcillin dose was 13.5 g (±6.5) per day. No significant differences occurred in liver function tests, white blood count, and platelet count from baseline. Serum creatinine showed a statistically significant decrease from baseline.
Conclusions: Higher than FDA approved doses of ticarcillin–clavulanate may be safely used in the treatment of exacerbations in pediatric cystic fibrosis patients.

Keywords: Antibiotics; Cystic fibrosis; Pediatrics; Ticarcillin–clavulanate; Safety

1. Background

Ticarcillin–clavulanate (Timentin®) is a combination semi-synthetic beta-lactam antibiotic (ticarcillin) and beta-lactamase inhibitor (clavulanate) for intravenous (IV) administration. It is commonly used in the treatment of infections caused by susceptible aerobic gram positive, aerobic gram negative (i.e. *Pseudomonas aeruginosa*) and anaerobic bacteria [1]. The Cystic Fibrosis Foundation (CFF) recommends that the empiric treatment of pulmonary exacerbations should include two anti-pseudomonal antibiotics with different mechanisms of action (i.e. anti-pseudomonal beta-lactam plus aminoglycoside) to reduce the chance of developing resistance [2].

The Intermountain Cystic Fibrosis Pediatric Center has utilized ticarcillin–clavulanate (400 mg/kg/day divided every 6 h, up to a maximum dose of 24 g/day of the ticarcillin component) as the first line anti-pseudomonal agent in conjunction with tobramycin (10–12 mg/kg/day) since 1994. Multiple reasons exist for ticarcillin–clavulanate to serve as the first line agent:

- 90% of *P. aeruginosa* isolates in 2009 were susceptible to ticarcillin–clavulanate [3]
- Less risk association with new methicillin-resistant *Staphylococcus aureus* (MRSA) infections versus ceftazidime [4,5]
- High rates of serum sickness with piperacillin/tazobactam [6,7]
- Less expensive than ceftazidime, piperacillin/tazobactam, meropenem, aztreonam, and imipenem/cilistatin [8].

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This ticarcillin–clavulanate dosing strategy has recently been brought into question since it differs from the CFF recommendations and the Food and Drug Administration (FDA) approved package labeling.

- CFF dosing recommendation [9,10]
  - 400 mg/kg/day divided every 6 h, (max 12 g/day)
- Ticarcillin–clavulanate FDA approved package labeling [1]
  - Mild to moderate infections—200 mg/kg/day divided every 6 h
  - Severe infections (patients < 60 kg)—300 mg/kg/day divided every 4 h
  - Mild to moderate infections (patients > 60 kg)—3 g every 6 h (maximum 12 g/day)
  - Severe infections (patients > 60 kg)—3 g every 4 h (maximum 18 g/day).

Multiple dosing references and studies have been published suggesting an alternative ticarcillin–clavulanate dosing strategy is preferred in cystic fibrosis (CF) patients (Table 1). No severe adverse events were reported in the published studies utilizing alternative dosing strategies that differ from the FDA approved dosing strategy. The main purpose of this study is to determine the safety profile of a higher than FDA approved dosing strategy by analyzing specific laboratory parameters.

2. Methods

This was a retrospective database study of de-identified pediatric CF patients admitted from January 1, 2005 to December 31, 2009 to Intermountain Primary Children's Medical Center. To be included in the study, patients received ticarcillin–clavulanate 400 mg/kg/day divided every 6 h (maximum 24 g/day of ticarcillin component) for at least 7 days, and have recorded baseline and follow-up laboratory data (i.e. serum creatinine, liver function tests, white blood count (WBC), and platelet count). Follow-up laboratory data were drawn >4 days after starting ticarcillin–clavulanate therapy. Patients were excluded from the study if they received <7 days of ticarcillin–clavulanate therapy, or did not have any follow-up

Table 1
Summary of ticarcillin/clavulanate studies and dosing references.

Studies		
Reference	Ticarcillin–clavulanate dosing strategy (ticarcillin component)	Adverse effects
Ervin and Bullock [11]	400 mg/kg/day	Prolongation of bleeding time in 1 patient who received 400 mg/kg/day
Nelson et al. [12]	400 mg/kg/day	Mild eosinophilia of 6–7% occurred in 3 children who received 400 mg/kg/day Alkaline phosphatase levels did not rise 3 children had transient elevations in Aspartate Transferase (AST) (50–81 IU) 1 child had microscopic hematuria Blood Urea Nitrogen (BUN) and serum creatinine (SCr) levels remained within normal limits No rashes attributable to ticarcillin reported
Conway et al. [13]	2 groups: 1st: Mean 468 mg/kg/day (range 249–762 mg/kg/day) 2nd: Mean 586 mg/kg/day (range 186–620 mg/kg/day)	Non-significant fall in absolute neutrophil count (ANC) and platelet count in both groups No changes in BUN, SCr, and electrolytes were noted
Horrevorts et al. [14]	600 mg/kg/day	No change in SCr
Schaad et al. [15]	500 mg/kg/day	Slight urticaria occurred in 1 patient No significant changes in BUN, creatinine, urinalysis, or hematological parameters occurred Transient 3 fold increases in transaminases occurred in 2 patients in ticarcillin group Alkaline phosphatase significantly decreased in the ticarcillin group
De Groot et al. [16]	120 mg/kg × 1 dose	None reported
Dosing references		
Nelson Textbook of Pediatrics 18th Edition [17]	Ticarcillin/clavulanate dose for CF: 400 mg/kg/day divided every 6 h (max 24 g/day)	N/A
Red Book 29th Edition; 2009 Report of the Committee on Infectious Diseases; The American Academy of Pediatrics [18]	Severe Infections: 200–300 mg/kg/day in 4 divided doses (max 12–24 g/day)	N/A
Lexi-Comp Pediatric Dosage Handbook [19]	Severe infections: 400 mg/kg/day divided every 6 h (max 18–24 g/day)	N/A

laboratory parameters (i.e. serum creatinine, liver function tests, WBC, or platelet counts). Other variables examined include reported adverse reactions, susceptibility data, and culture status. The data were analyzed using descriptive statistics and Mann–Whitney *U* test (paired data with unequal variances) [20].

3. Results

155 patients (age: 0–19 years; weight: 3.45–71.2 kg) received ticarcillin–clavulanate 400 mg/kg/day from January 1, 2005 to December 31, 2009. 127 patients with 276 unique encounters met inclusion criteria. During this study time frame, 11,868 doses were received. 12 patients received 6 g every 6 h; 1 patient (68 kg) received 6.8 g every 6 h, and another (60 kg) patient received 24 g over 24 h. The remaining 113 patients received doses equaling 400 mg/kg/day up to 24 g of ticarcillin component/day. The mean (±SD) ticarcillin dose was 3.5 g (±2.16) every 6 h; while the mean (±SD) total ticarcillin dose was 13.5 g (±6.5) per day. The mean (±SD) length of hospital stay was 13.1 (±6.5) days. The baseline and follow-up laboratory parameters, reported adverse effects, and microbiological results are summarized in Table 2. The safety parameters showed no statistically significant differences from baseline (p=NS) except for serum creatinine (for all patients and in those who received ≥12 g of ticarcillin component/day). The serum creatinine values showed a statistically significant decrease from 0.55 (±0.18) g/dL at baseline to 0.47 (±0.19) g/dL at follow-up ($p<0.05$). Reported adverse effects include arthralgias, rash, acute elevation of liver function tests, hematuria, and anaphylaxis. The ticarcillin–clavulanate susceptibility in *P. aeruginosa* isolates increased during the course of the study (82% to 90%), and 53 patients cultured positive for a new organism on cultures subsequent to a course of ticarcillin–clavulanate.

Table 2
Summary of laboratory parameters, adverse effects, and microbiology.

Laboratory parameter	Baseline (mean±SD)	Follow-up (mean±SD)	p-value
Serum creatinine (g/dL)—all patients	0.55±0.18	0.47±0.19	p=0.001
Serum creatinine (g/dL)—patients receiving ≥12 g/day	0.65±0.17	0.59±0.17	p=0.012
ALT (median)—all	25 (5 to 257)	33 (6 to 320)	p=NS
ALT (median)—patients receiving ≥12 g/day	24 (5 to 257)	33 (6 to 320)	p=NS
AST (median)—all	40.5 (18 to 429)	40 (14 to 232)	p=NS
AST (median)—patients receiving ≥12 g/day	40.5 (18 to 117)	40 (14 to 232)	p=NS
WBC (median)—all	9.7 (2.6 to 48.4)	8.8 (3.1 to 60.9)	p=NS
WBC—patients receiving ≥12 g/day	9.3±4.3	8.3±4.6	p=NS
Platelets—all	292±105	274±123	p=NS
Platelets—patients receiving ≥12 g/day	277±99	276±126	p=NS

Reported adverse effects

Adverse effects	Number of patients
Hematuria and anaphylaxis	1
Acute elevation of liver function tests	1
Arthralgia	2
Rash	1

Microbiological effects—susceptibility data

Ticarcillin–clavulanate susceptibility rate for *Pseudomonas aeruginosa* (2005–2009)	Year
82%	2005
80%	2006
88%	2007
92%	2008
90%	2009

Microbiological effects—emergence of resistant organisms

Organism	Number of patients
Methicillin-resistant *S. aureus* (MRSA)	19[a]
S. maltophilia	34[a]
B. cepacia	0

[a] 6 of these patients cultured positive for both MRSA and *S. maltophilia*.

4. Discussion

The purpose of performing this retrospective chart review was to validate the safe use of higher than FDA approved doses of ticarcillin–clavulanate in a pediatric CF population. The Intermountain Cystic Fibrosis Pediatric Center has been using ticarcillin–clavulanate as its first line anti-pseudomonal beta-lactam, and the dosing strategy of 400 mg/kg/day divided every 6 h (maximum 24 g/day of ticarcillin component) for over 15 years. It was not until late 2009, that a discrepancy was noted between pediatric, package insert, adult, and CFF dosing regimens. These questions lead to an investigation into the basis of the dosing recommendations in the standard dosing references. An extensive literature search was performed that lead to the discovery of several older studies showing the safe and effective use of higher than approved doses of ticarcillin–clavulanate in CF and non-CF patients (Table 1).

To our knowledge, this is the largest retrospective study analyzing the safety of high dose ticarcillin–clavulanate in pediatric CF patients. The mean doses of 3.5 g every 6 h, maximum 13.5 g/day (ticarcillin component), are higher than the FDA approved dose of 3 g every 6 h, maximum 12 g/day (ticarcillin component). Our results are consistent with the dosage recommendations provided by De Groot and colleagues [16]. The only safety parameter that showed a statistically significant difference was serum creatinine. We felt that this was clinically significant because these patients were receiving high dose ticarcillin–clavulanate along with another known nephrotoxic agent, intravenous tobramycin. Adverse reactions, ranging from rash to anaphylaxis occurred in five patients who received the study regimen. Although these reactions are listed in the package insert, their true causality in this study cannot be determined retrospectively.

Clinical efficacy parameters (susceptibility patterns of ticarcillin–clavulanate in *P. aeruginosa*, and the acquisition of new organisms) were also examined. The susceptibility rate to ticarcillin–clavulanate in *P. aeruginosa* improved from 2005 to 2009. 34% of participants cultured positive for a new organism.

Improvement in susceptibility may be a positive result; however, concern exists with the number of newly acquired cases of *S. maltophilia*, since ticarcillin–clavulanate has been associated with acquisition of this organism [9]. The causality of the relationship between the microbiological results and high dose ticarcillin–clavulanate also cannot be determined based on the retrospective study design.

In addition to the causality limitations already mentioned, another study limitation is that the only patients that were included in the study were those who had follow-up laboratory monitoring.

Based on the study results, we conclude ticarcillin–clavulanate 400 mg/kg/day divided every 6 h (maximum 24 g of ticarcillin component/day) appears to be safe and well-tolerated by the majority of CF patients who receive it for pulmonary exacerbations. More studies of this dosing regimen are needed in order to fully answer the clinical effects (i.e. clinical response rate) and causality of adverse reactions and microbiological effects.

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